

ORIGINAL ARTICLE

Glycemic index, cholecystokinin, satiety and disinhibition: is there an unappreciated paradox for overweight women?

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Background: The clinical utility of a low glycemic index (LGI) diet for appetite and food intake control is controversial. Complicating the issue are psychological and behavioral influences related to eating.

Objective: The aim of this study was to investigate the satiety and glycemic response to high GI (HGI) and LGI meals in overweight restrained (R, $n = 12$) and unrestrained (UR, $n = 10$) women.

Design and measurements: In a randomized crossover study, subjective satiety, cholecystokinin (CCK), glucose, insulin, triacylglyceride (TG) and free fatty acids (FFAs) were measured at defined intervals for 8 h after the participants consumed HGI or LGI test meals. Test meals were matched for energy, energy density, macronutrient content and available carbohydrate, but differed by carbohydrate source; refined grain versus whole grain, respectively.

Results: The HGI meal resulted in greater satiety overall, suppressing hunger, desire to eat and prospective consumption compared with the LGI ($P < 0.01$) meal. Plasma CCK was significantly elevated after the HGI meal compared with the LGI meal ($P < 0.001$). Plasma glucose, insulin and TG were higher and FFAs were lower after the HGI meal compared with the LGI meal ($P < 0.001$). Dietary restraint did not significantly influence CCK ($P = 0.14$) or subjective satiety ($P > 0.4$); however, an interaction of restraint and disinhibition on CCK was apparent. CCK was blunted in R participants with higher disinhibition scores than UR or R participants with lower disinhibition scores ($P < 0.05$).

Conclusions: A LGI diet may not be suitable for optimal satiety and appetite control in overweight women. The relationship between cognitive influences of eating and biobehavioral outcomes requires further investigation.

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Introduction

The glycemic index (GI) is suggested as a useful strategy for achieving and maintaining a healthy body weight.^{1,2} However, variability among dietary components, energy status and experimental design challenge scientific agreement as to the effectiveness of GI. GI of a food is defined as the incremental area under the plasma glucose response curve of a 50 g carbohydrate portion of a test food expressed

as a percentage of the response to the same amount of carbohydrate from a reference food: usually white bread or glucose solution.³ Carbohydrate-rich foods raise blood glucose concentrations more so than fat- or protein-rich foods, and hence, recent dietary trends promote higher levels of protein intake, touting the threat of carbohydrates to metabolic control and energy balance.

The claimed benefits of low GI (LGI) foods and diets include greater control of appetite, body weight, blood glucose, insulin and cholesterol, resulting in reduced risk for type 2 diabetes mellitus, cardiovascular disease and prevention and management of obesity.^{4–8} Long-term studies, however, have reported no difference in weight loss between LGI and high GI (HGI) diets.^{9–12} Benefits in the maintenance of weight loss also seem questionable. In an 18-month study, comparing LGI and HGI diets, higher rates of body weight regain were observed on the LGI diet after maximal weight

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loss compared with the HGI diet group ($P = 0.11$).¹⁰ Evaluation of hunger and other satiety indicators in short- and long-term dietary intervention studies is variable.^{10,13,14} Even with simple preparations of glucose and fructose with distinct glycemic responses, satiety was greater after the glucose load than fructose load.¹⁵ Inconsistent associations between GI and body mass index have also been reported.⁷ Hence, the role of GI diets in managing appetite/satiety and overall body weight remains a debated topic.

Many dietary factors influence GI, including food processing, food matrix, nutrient bioavailability and the interaction of nutrients within the meal itself. These same factors also influence the rate and capacity of digestion and absorption. Digestive and absorptive mechanisms are tightly regulated by hormonal responses, such as cholecystokinin (CCK) and insulin. These peripherally derived signals are sensitive to incoming dietary composition and help to orchestrate and direct information between and along the gut-brain axis to allow for optimal use, metabolism and storage of nutrients from the diet. These signals also serve as critical indicators of short- and long-term energy needs. In this way, endocrine responses to food intake are critical for meal-to-meal food intake regulation and overall energy homeostasis.

Both homeostatic and nonhomeostatic systems are involved in food intake. It has been suggested that the rise in obesity may be, at least in part, because of the activation of nonhomeostatic, food reward centers in the brain that override hormonal regulation of food intake.^{16,17} Cognitive dietary restraint is a pattern of attempted weight control characterized by cognitive restriction of food intake that has paradoxically been linked with overeating and/or weight gain.¹⁸

We had reported earlier that the patterns of eating coincident with cognitive dietary restraint suppress the gut hormone response to a test meal intermediate in glycemic load in normal weight men and women.¹⁹ The aim of this study was to investigate the relationship of GI, satiety and biological response patterns of key mediators of short-term food intake in a population of restrained (R) and unrestrained (UR) overweight women. The primary working hypothesis was that the satiety effect of LGI and HGI meals will be determined by the biological response patterns and that women exhibiting high dietary restraint will be less responsive to satiety cues.

Methods

The Human Subjects Research Committee of the University of California, Davis, approved the study. The study was conducted in accordance with the Helsinki Declaration of 1975 as revised in 1983. All participants signed a written informed consent form before any study-related procedures were performed.

Participants

Twenty-five nonsmoking women between 20 and 50 years of age participated in this study after passing the initial health screening consisting of medical history, clinical blood chemistries and blood pressure measurements. All volunteers were overweight with body mass index in the range of 25.0–29.9 kg/m². Volunteers were excluded if they had indications of cardiovascular or metabolic disorders, were pregnant or had been pregnant within 18 months before the study and/or were taking medications or herbal supplements to manage body weight or control appetite. Volunteers agreed to remain weight stable during the period of the study and refrain from remarkable changes in diet and habitual physical activity level. In general, participants were requested to maintain current dietary and physical activity patterns. Upon entry into the study, the participants completed the Three Factor Eating Questionnaire²⁰ to characterize the participants on the levels of dietary restraint and disinhibition. Cognitive restraint was based on factor 1 scores of more than 10. Disinhibition was based on factor 2 scores of more than 7. The study reported here is a component of a larger metabolic study of which portions have been published earlier.^{21,22} The final analysis of this report includes 22 of the original 25 participants enrolled. This is because of a protocol amendment to increase sample volume to accommodate the CCK analysis after the first three participants had been studied. The results of this study are based on the 22 participants enrolled after the amendment.

Study design

The study was a two-arm, two-sequence, randomized cross-over design to characterize the satiety response to two breakfast meals defined on the basis of GI: HGI breakfast meal versus LGI breakfast meal. Satiety response was determined by measured changes in subjective satiety (that is, ratings of hunger, fullness, desire to eat and prospective consumption) and plasma CCK from baseline (fasting state) to 8 h post-breakfast consumption. Changes in glucose, insulin, triacylglycerides (TGs) and free fatty acids (FFAs) were also measured. All volunteers participated in both treatment arms, each time during the follicular phase of their menstrual cycle. Each 8-h-study day was preceded by a 3-day diet run-in period consisting of foods (all provided) that corresponded to the breakfast meal to be served on the study 'test' day (day 4).

Diets and test meal

Breakfast test meals and treatment-control run-in diets were created using the computer software ProNutra (Princeton Multimedia Technologies, Princeton, NJ, USA). Breakfast test meals and run-in diets had similar macronutrient content with carbohydrate:protein:fat ratio of 56:14:30 as a percentage of energy (Table 1). Major differences in the breakfast test meals (HGI versus LGI)

and diet run-ins were carbohydrate source (refined versus whole grains carbohydrate options), fiber content and calculated GI and glycemic load. Breakfast test meals were prepared from all commercially available foods. The LGI breakfast meal consisted of bran cereal, reduced fat milk and fruited yogurt. The HGI breakfast test meal included rice/corn cereal, reduced fat milk and fruited yogurt. Small quantities of isolated whey protein and cream were added to the test meals to equalize the protein and fat contents, respectively. All food was provided by and prepared in the metabolic research kitchen of the Ragle Human Nutrition Research Center at the University of California, Davis campus.

Study protocol

On study 'test' days, participants arrived at the laboratory between 0700 and 0800 hours, following an overnight fast. Body weight and height were measured with the participant wearing a surgical scrub outfit of a known weight and no shoes using an electronic scale (Val-Del Scale Co., Rancho Cordova, CA, USA) and stadiometer (Model S100, Ayrton Corp, 134 Prior Lake, MN, USA). Body mass index was calculated by using weight and height measures. Body composition was determined by dual-energy X-ray absorptiometry using a whole body scan (Lunar Prodigy, GE Medical Corp., Madison, WI, USA). Analysis was performed using software version 2.05. Following these measurements, a nurse inserted an antecubital indwelling catheter and let the participant rest comfortably and quietly for approximately 30 min. During this time, procedures for calibrating the gas analyzers in the metabolic cart were performed. After the participant had rested for 30 min, they were asked to rate their level of hunger, fullness, desire to eat and prospective consumption on visual analog scales (VAS) administered through a handheld palm pilot, the Palm Zire 21 (Sunnyvale, CA, USA). Thereafter, a measurement of resting energy expenditure was taken by collecting expired gases for 20 min to determine oxygen consumption ($l\ min^{-1}$, VO_2) and carbon dioxide production ($l\ min^{-1}$, $145\ VCO_2$). Following this measurement, the first fasting blood sample was obtained and a second rating of subjective satiety rating was collected. After a 20-min rest, a second 20-min gas collection was carried out. Following this sequence of gas collection–blood draw–gas collection, the participant rated their state of hunger and satiety and was then given the scheduled breakfast test meal. Participants consumed the meal within 15 min, and over the subsequent 8 h, respiratory gases were collected for 20 min intervals, subjective ratings of satiety were collected and the blood samples were drawn. Time points for rating satiety followed by the blood sampling for CCK analysis were time (T)30, T60, T90, T120, T150, T210, T270, T360 and T480 min following the breakfast test meal, and the participant rested quietly throughout this 8-h time period in a semi-reclined position.

Table 1 Composition of run-in diets^a and breakfast test meals^b

Diet information	High glycemic index (HGI)		Low glycemic index (LGI)	
	Run-in Diet	Breakfast Test meal	Run-in Diet	Breakfast Test meal
Energy (kcal)	2091	833	2106	835
Carbohydrate (%)	56.4	54.2	56.5	54.6
Protein (%)	13.9	15.0	13.9	14.7
Fat (%)	29.7	30.8	29.5	30.7
Fiber (g)	9.9	2.4	46.6	35.5
Glycemic index ^c	76.6	76.7	42.5	36.5

Reproduced with permission from Motton *et al.*²² ^aRun-in diet values reported as an average of intake per day, based on an energy intake prescription of $2100\ kcal\ day^{-1}$. The energy content of the run-in diet was adjusted on an individual basis to meet the individual's daily energy requirement for weight maintenance. ^bBreakfast test meal values represent an energy intake prescription of $2100\ kcal\ day^{-1}$. The energy content of the test meal was adjusted on an individual basis and provided 40% of the individual's daily energy requirement for weight maintenance. The amounts of food served in the test meal were adjusted proportionately to maintain the same macronutrient ratios at all energy levels. ^cGlycemic index values are based on the glucose standard and represent an average weight by available carbohydrate in each food item constituting the test meal or run-in diet.

Analyses

Subjective satiety was assessed using VAS methodology applied to and administered through a Palm Zire 21 (Sunnyvale). Participants rated their levels of hunger, fullness, desire to eat, prospective consumption, nausea, thirst and satisfaction of preload on-line scales shown on the PDA screen. Questions such as 'how hungry do you feel right now?' or 'how strong is your desire to eat right now?' preceded a line anchored by opposing phrases 'not at all' and 'extremely'. Other anchors consisted of the phrases 'none' and 'extremely large amount' to assess prospective consumption. Use and value of these scales for assessing motivation to eat and food preference have been reported earlier.¹⁹

Blood samples were collected in EDTA coated vacutainer tubes (for CCK and TG analyses) and in sodium fluoride/potassium oxalate vacutainer tubes (for glucose analysis), immediately cooled in ice, and plasma was obtained by centrifugation (Centra CL3R centrifuge, International Equipment Co., Chattanooga, TN, USA) at $1300g$ for 10 min at $23^{\circ}C$. Three 1 ml aliquots of plasma + aprotinin (protease inhibitor) were frozen at $-80^{\circ}C$ for the determination of CCK concentrations by radioimmunoassay. Other aliquots ($\sim 1\ ml$) of plasma were stored in microcentrifuge tubes and frozen at $-80^{\circ}C$ for subsequent analysis of glucose and TG. Blood samples were also drawn into vacutainers with no additives, allowed to sit at room temperature for $\sim 20\ min$ to allow for clotting, and centrifuged at $1300g$ for 10 min at $23^{\circ}C$. Aliquots ($\sim 1\ ml$) of serum were transferred to microcentrifuge tubes and frozen at $-80^{\circ}C$ for analysis of insulin and FFAs concentrations.

Plasma CCK was measured by commercial RIA kit purchased from Immuno-Biological Laboratories Inc. (Minneapolis, MN, USA kit number RB 302). This kit uses a highly specific and selective antibody for the bioactive CCK in plasma and has been used earlier in our lab.¹⁹

Plasma glucose was determined through an enzymatic assay (Roche Diagnostics Corp., Indianapolis, IN, USA) using a Hitachi Automatic Analyzer (Boehringer Mannheim Corp., Indianapolis, IN, USA). Insulin was determined through a solid-phase, two-site, chemiluminescent enzyme-labeled immunometric assay using an Immulite analyzer (Diagnostic Products Corp., Los Angeles, CA, USA). TGs and FFAs were analyzed using enzymatic assays (Roche Diagnostics Corp., and Wako Chemicals USA Inc., Richmond VA, USA, respectively). These assays were adapted for the Hitachi Automatic Analyzer.

Laboratory analysis was performed in batches according to the Standardization Program of the US Centers for Disease Control and Prevention and the National Heart Lung and Blood Institute.

Statistical analysis

Data were analyzed by repeated measures analysis of variance using PC-SAS (version 8.2; SAS Institute Inc., Cary, NC, USA), GLM and MIXED procedure with breakfast meal and time as main factors, and participant as the blocking variable. Data analyzed from the VAS were first converted to increments above baseline to account for relative baseline variability among participants. Substrate metabolites not conforming to expected distributional assumptions were log transformed and noted accordingly. Significant differences among treatment means were analyzed by pairwise *t*-test and Tukey's honestly significant test for appropriate comparisons. The level used to determine statistical significance was $P < 0.05$.

Results

Participant characteristics

Twenty-two women participated in the study. Mean (\pm s.d.) age (years), body mass index (kg/m^2), percent body fat were 31 ± 8 years, 27 ± 1 and $39 \pm 3\%$, respectively. All participants maintained their body weight within 1.0 kg throughout the study.

Twelve women met criteria for cognitive restraint (scores > 10 on the Three Factor Eating questionnaire (factor 1);²⁰ mean \pm s.d., 13.5 ± 2.7) and 10 participants were characterized as UR (mean score, 6.5 ± 2.3). Mean scores for disinhibition (factor 2) and hunger (factor 3) were 7.6 ± 3.0 and 4.6 ± 2.8 , respectively.

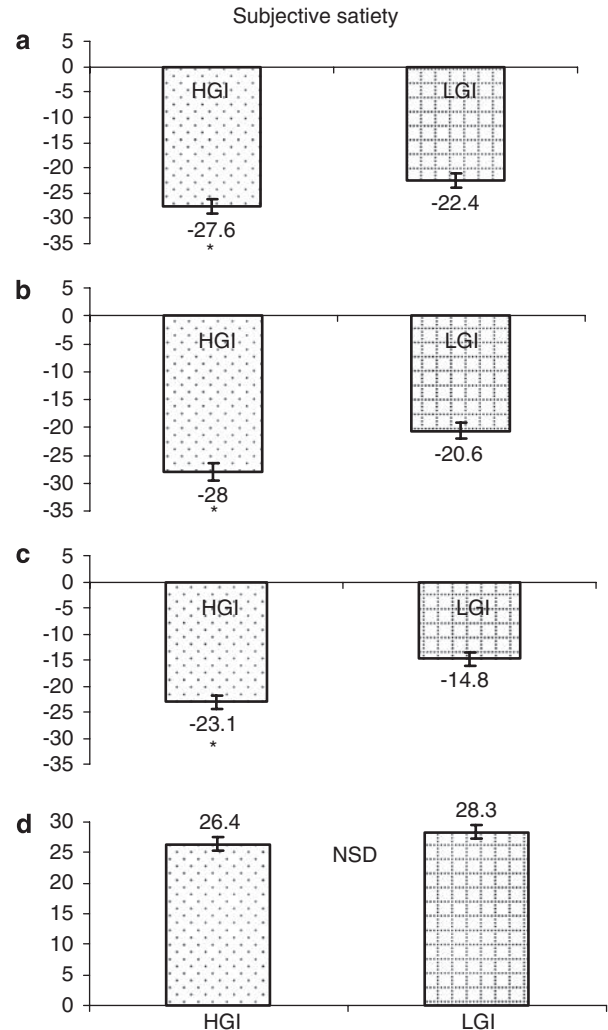


Figure 1 (a–d) Subjective satiety responses to high glycemic index (HGI) and low glycemic index (LGI) meals in overweight women. Values are the least squares means \pm s.e.m. of response (0–480 min), $n = 22$. Fasting baseline values for hunger, desire to eat, prospective consumption and fullness were 57.9 ± 2.2 , 56.1 ± 2.4 , 58.2 ± 2.0 and 11.4 ± 1.9 , respectively. Figures represent main effects of meal ($P < 0.009$, except for fullness, $P > 0.2$) and time ($P = 0.0001$). Significant differences in subjective satiety response to meals among women are indicated by asterisk symbol. NSD, not significantly different. (a) hunger, (b) desire to eat, (c) prospective consumption and (d) fullness.

Subjective satiety (VAS)

In overweight women, the HGI meal suppressed hunger by approximately 20% more than the LGI meal (Figure 1a, $P = 0.009$). Similarly, the HGI meal induced a greater suppression on desire to eat and prospective consumption compared with the LGI meal (26 and 36% more respectively, $P = 0.007$ and $P = 0.001$, Figures 1b and c). There was no difference in the ratings of sensation of fullness ($P > 0.2$, Figure 1d) between HGI and LGI meals in participants. Overweight women given a HGI meal were more satiated than those given an LGI meal.

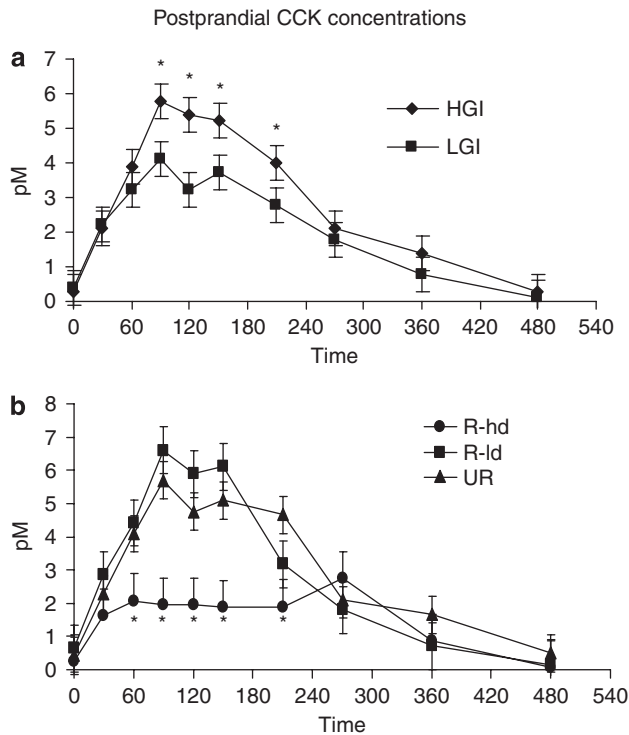


Figure 2 (a and b) CCK responses to high glycemic index (HGI) and low glycemic index (LGI) meals in overweight women (a) and CCK response to meals in women according to eating disposition scores from the Three Factor Eating Questionnaire: restrained—high disinhibition (R-hd), restrained—low disinhibition (R-ls) and unrestrained (UR) (b). Values are the mean \pm s.e.m. for each time point (0–480 min), $n=22$. Figures represent main effects of meal, time and patient characteristic by time interaction ($P=0.0001$, $P=0.002$ and $P=0.01$, respectively). Asterisk symbol indicates a significant concentration difference at the specified time point.

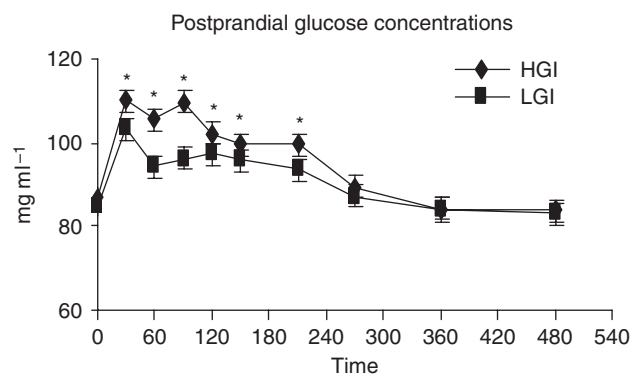


Figure 3 Glucose responses to high glycemic index (HGI) and low glycemic index (LGI) meals in overweight women. Values are the mean \pm s.e.m. for each time point (0–480 min), $n=22$. Figure represents main effects of meal and time ($P<0.0001$ and $P<0.0001$, respectively). Asterisk symbol indicates a significant concentration difference at the specified time point.

Biochemical analysis

The effects of diet on CCK, glucose, insulin, TG and FFAs responses are shown in Figures 2a and 3–6. CCK was measured as the primary mediator of satiety. The main

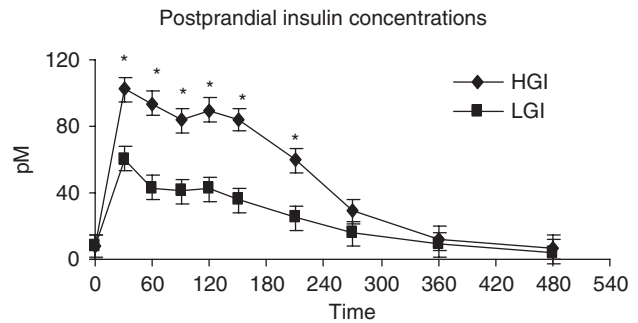


Figure 4 Insulin responses to high glycemic index (HGI) and low glycemic index (LGI) meals in overweight women. Values are the mean \pm s.e.m. for each time point (0–480 min), $n=22$. Figure represents main effects of meal and time ($P<0.0001$ and $P<0.0001$, respectively). Asterisk symbol indicates a significant concentration difference at the specified time point.

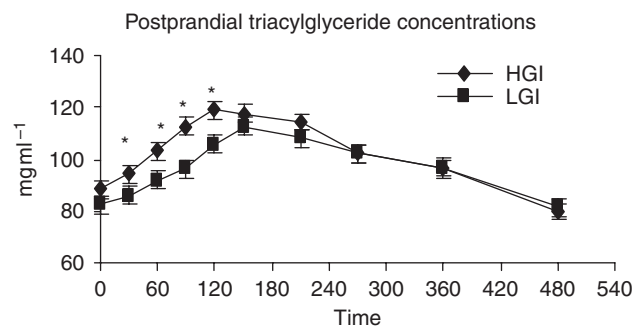


Figure 5 Triacylglyceride responses to high glycemic index (HGI) and low glycemic index (LGI) meals in overweight women. Values are the mean \pm s.e.m. for each time point (0–480 min), $n=22$. Figure represents main effects of meal and time ($P<0.0001$ and $P<0.0001$, respectively). Asterisk symbol indicates a significant concentration difference at the specified time point.

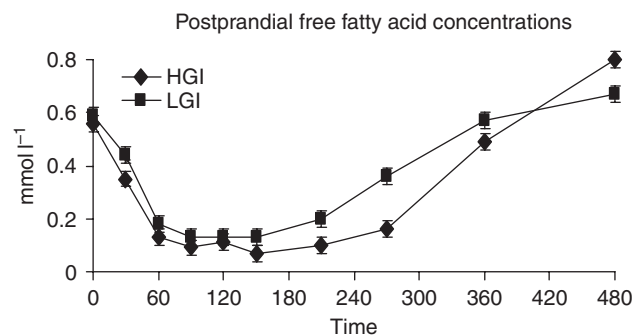


Figure 6 Free fatty acid (FFA) responses to high glycemic index (HGI) and low glycemic index (LGI) meals in overweight women. Values are the mean \pm s.e.m. for each time point (0–480 min), $n=22$. Figure represents main effects of meal and time interaction ($P<0.001$ and $P<0.0001$, respectively). Asterisk symbol indicates a significant concentration difference at the specified time point.

effects of meal and time were evident ($P=0.0001$ and $P=0.002$, respectively). Both meals induced a significant increase in plasma CCK from baseline (Figure 2a). However,

by the 90 min blood draw, a significant separation in concentration time curves was apparent, favoring higher CCK with the HGI meal. By 4.5 h, concentrations of CCK in response to the LGI and HGI meals were not different. Consistent with the pattern of response, the area under the CCK response curve (AUC) was significantly greater after consumption of the HGI meal compared with the LGI meal ($P < 0.05$) in these overweight women.

In addition to the elevated CCK, the HGI meal also produced higher concentrations of glucose, insulin, and TGs and lower FFAs than the LGI meal ($P < 0.0001$, Figures 3–6). Glucose and insulin concentrations rose immediately with consumption of meals, and the meal-associated concentration differences were apparent at the 30 min blood sample (glucose: 110 ± 2.7 versus 103 ± 2.6 mg per 100 ml, $P < 0.05$; insulin: 102 ± 7.1 versus 60 ± 7.3 pmol l⁻¹, respectively $P < 0.05$). By 4.5 h, both glucose and insulin concentrations in response to the meals were no longer different (Figures 3 and 4). The plasma TG response to the LGI meal seemed delayed compared with the HGI meal (Figure 5). For the first 150 min, plasma TG concentrations were significantly lower after the LGI meal compared with the HGI meal ($P < 0.05$). Thereafter, concentrations were not different from 2.5 to 8 h. Serum FFAs were significantly lower after the HGI meal (least square mean as estimate of response 0.286 ± 0.010 and 0.340 ± 0.009 mmol l⁻¹ for HGI and LGI, respectively, $P < 0.001$ (76.9 ± 2.7 and 91.5 ± 2.4 mg l⁻¹)). The time concentration curve is shown in Figure 6 illustrating the meal by time interaction ($P < 0.0001$).

Biobehavioral interactions

Dietary restraint did not influence plasma CCK concentrations in response to meals; however, among R participants, those with higher disinhibition scores (scores of > 7) had a blunted CCK response to both meals (R—high disinhibition, CCK pM = 1.6 ± 0.6 , R—low disinhibition, CCK pM = 3.2 ± 0.5 , UR CCK pM = 3.1 ± 0.4 ; $P < 0.05$). The time concentration curve of this response is shown in Figure 2b. Disinhibition alone was not significant ($P > 0.4$). Interaction between endocrine responses to test meals and cognitive dietary restraint did not influence perceived satiety as measured by VAS.

Discussion

The primary objective of this study was to investigate the relationship of GI, satiety and biological response patterns of key mediators of short-term food intake in a population of R and UR overweight women. We have shown earlier that dietary restraint blunts the CCK response to meals in healthy weight men and women. We were interested in extending these findings using GI distinct meals in an overweight female population characterized by R or UR eating behavior

and further testing the relationship with subjective satiety. Although cognitive dietary restraint as a main factor did not influence satiety outcomes in this study of all women, disinhibition among R eaters surfaced as a potential factor in the CCK response to meals. Overweight women with high disinhibition scores within the construct of dietary restraint had a lower overall CCK response to the test meals than either the R participants with low disinhibition scores or the participants who scored as UR. To the best of our knowledge, this is the first report of an interaction of dietary restraint and disinhibition on endocrine responses, namely CCK, to food intake. Dietary restraint describes the tendency to control consciously food intake to prevent weight gain or to achieve weight loss, whereas disinhibition refers to the breakdown of this cognitive control. Overeating, disordered eating, particularly binge eating disorder and bulimia nervosa, weight gain and weight regain after weight loss is associated with the higher disinhibition scores both in clinical and nonclinical individuals.^{23–27} Moreover, it seems that the severity of eating pathology is associated with high disinhibition scores together with high restraint scores, suggesting that the conflict of high disinhibition in the presence of restraint is important in the dysregulation of eating.²⁷ A biological basis in support of these findings has only been vague with conflicting reports on leptin and ghrelin,^{28–30} and there is no information on postprandial satiety signaling. The blunted CCK response that we report here is of interest in light of data indicating that postprandial CCK is blunted in bulimia nervosa and restored with successful treatment. Our data provide a biological basis for progression and persistence of disordered eating, and may serve to confirm successful treatment therapy targeting reductions in disinhibition, and possibly reduce relapse, especially since changes in the Three Factor Eating Questionnaire scoring are minimal during recovery. These findings warrant replication as well as future research in identifying patterns of released satiety signals corresponding to food intake patterns associated with behavioral and psychological correlates that promote unfavorable changes in food intake and body weight.

In addition to our findings of CCK, disinhibition and restraint, we also found that in overweight women, a HGI breakfast meal provided greater overall satiety than a LGI breakfast meal. These data are in contrast to the current dogma of eating LGI meals, where LGI is expected to be superior to HGI eating in managing appetite and body weight. Although the LGI meal provided for lower postprandial concentrations of glucose, insulin and TGs, consistent with the claims of LGI,^{31,32} it did not induce greater satiety. Rather, the higher ratings of hunger, desire to eat and prospective consumption after the LGI meal were associated with a lower CCK secretory response compared with the HGI meal. One possible explanation is the proposed relationship between circulating postprandial metabolic factors and CCK, in which higher circulating FFAs results in lower CCK concentrations.³³ In this study, the LGI meal was associated

with higher circulating FFAs; however, the magnitude of difference among meals was not as robust as one might expect to explain the difference in CCK. Nonetheless, the concept is modestly supported in this study and deserves follow up to better understand the metabolic influence on CCK release in response to meals.

In humans, fat is a potent stimulator of CCK followed by protein and then carbohydrate, all of which were matched in the two treatment meals. However, dietary fiber was not matched. The LGI meal contained 10-fold more fiber than the HGI meal. Directly, dietary fiber does not seem to stimulate CCK release. However, its action in the gut, dependent on the physical-chemical properties of the ingested fiber with coexisting nutrients can modify CCK release.^{34,35} The fiber used in the LGI meal was predominantly insoluble (for example, cellulose). Insoluble sources of dietary fiber provide bulk to the diet and decrease transit time through the gastrointestinal tract. The stimulation of CCK release by nutrients is maximal in the duodenum diminishing with passage of nutrients through the jejunum as CCK-secreting I cells become scarce. Hence, factors hastening transit, such as insoluble fiber, may result in a reduced endocrine response from the upper small intestine including CCK. We suspect that this is a major reason for the reduced CCK response in the LGI meal. As women seem to be sensitive to intestinal phase satiety events, perhaps more so than gastric phase events (that is, distension) as we have seen in men,³⁶ the reduced CCK in the LGI meal translated to reduced sensations of satiety. No differences in fullness were reported among these women further supporting the importance of intestinal satiety for women. These data have important implications for devising meal plans for achieving and maintaining a healthy body weight. Individuals who are overweight and obese comprise the target population for weight-reducing diets. Long-term compliance and success of these diets depends greatly on managing appetite and hunger. Hence, dietary prescriptions focused on LGI methodology, at least with the use of insoluble fibers, may not be well suited for overweight women requiring strong satiety signaling.

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References

- 1 Mann J. Dietary carbohydrate: relationship to cardiovascular disease and disorders of carbohydrate metabolism. *Eur J Clin Nutr* 2007; **61**: S100–S111.
- 2 Thomas D, Elliott E, Baur L. Low glycaemic index or low glycaemic load diets for overweight and obesity. *Cochrane Database Syst Rev* 2007; **18**: CD005105.
- 3 Brouns F, Bjorck I, Frayn K, Gibbs A, Lang V, Slama G *et al*. Glycemic index methodology. *Nutr Res Rev* 2005; **18**: 145–171.
- 4 Jenkins DJ, Wolever TM, Collier GR, Ocana A, Rao AV, Buckley G *et al*. Metabolic effects of a low-glycemic-index diet. *Am J Clin Nutr* 1987; **46**: 968–975.
- 5 Willett W, Manson J, Liu S. Glycemic index, glycemic load, and risk of type 2 diabetes. *Am J Clin Nutr* 2002; **76**: 274S–280S.
- 6 Bouche C, Rizkalla SW, Luo J, Vidal H, Veronese A, Pacher N *et al*. Five-week, low-glycemic index diet decreases total fat mass and improves plasma lipid profile in moderately overweight non-diabetic men. *Diabetes Care* 2002; **25**: 822–828.
- 7 Gaesser G. Carbohydrate quantity and quality in relation to body mass index. *J Am Diet Assoc* 2007; **107**: 1768–1780.
- 8 Brand-Miller JC, Holt SHA, Pawlak DB, McMillan J. Glycemic index and obesity. *Am J Clin Nutr* 2002; **76**: 281S–285S.
- 9 Aston LM, Stokes CS, Jebb SA. No effect of a diet with a reduced glycaemic index on satiety, energy intake and body weight in overweight and obese women. *Int J Obes* 2007; **32**: 160.
- 10 Sichieri R, Moura AS, Genelhu V, Hu F, Willett WC. An 18-mo randomized trial of a low-glycemic-index diet and weight change in Brazilian women. *Am J Clin Nutr* 2007; **86**: 707–713.
- 11 Raatz SK, Torkelson CJ, Redmon JB, Reck KP, Kwong CA, Swanson JE *et al*. reduced glycemic index and glycemic load diets do not increase the effects of energy restriction on weight loss and insulin sensitivity in obese men and women. *J Nutr* 2005; **135**: 2387–2391.
- 12 Sloth B, Krog-Mikkelsen I, Flint A, Tetens I, Bjorck I, Vinoy S *et al*. No difference in body weight decrease between a low-glycemic-index and a high-glycemic-index diet but reduced LDL cholesterol after 10-wk ad libitum intake of the low-glycemic-index diet. *Am J Clin Nutr* 2004; **80**: 337–347.
- 13 Ludwig D. Dietary glycemic index and the regulation of body weight. *Lipids* 2003; **38**: 117–121.
- 14 Bornet FRJ, Jardy-Gennetier A-E, Jacquet N, Stowell J. Glycaemic response to foods: Impact on satiety and long-term weight regulation. *Appetite* 2007; **49**: 535.
- 15 Akhavan T, Anderson GH. Effects of glucose-to-fructose ratios in solutions on subjective satiety, food intake, and satiety hormones in young men. *Am J Clin Nutr* 2007; **86**: 1354–1363.
- 16 Berthoud H-R, Morrison C. The brain, appetite, and obesity. *Annu Rev Psychol* 2008; **59**: 55–92.
- 17 Grill HJ, Skibicka KP, Hayes MR. Imaging obesity: fMRI, food reward, and feeding. *Cell Metab* 2007; **6**: 423.
- 18 Schur EA, Cummings DE, Callahan HS, Foster-Schubert KE. Association of cognitive restraint with ghrelin, leptin, and insulin levels in subjects who are not weight-reduced. *Physiol Behav* 2008; **93**: 706.
- 19 Burton-Freeman B. Sex and cognitive dietary restraint influence cholecystokinin release and satiety in response to preloads varying in fatty acid composition and content. *J Nutr* 2005; **135**: 1407–1414.
- 20 Stunkard AJ, Messick S. The three-factor eating questionnaire to measure dietary restraint, disinhibition and hunger. *J Psychosom Res* 1985; **29**: 71.
- 21 Keim N, Hembrooke T, Horn W, Gustafson M. Energy expenditure in response to meals based on whole grains vs refined grains. *Obesity* 2006; **14**: A172.
- 22 Motton D, Keim N, Tenorio F, Horn W, Rutledge J. Postprandial monocyte activation in response to meals with high and low glycemic loads in overweight women. *Am J Clin Nutr* 2007; **85**: 60–65.

- 23 Kensinger GJ, Murtaugh MA, Reichmann SK, Tangney CC. Psychological symptoms are greater among weight cycling women with severe binge eating behavior. *J Am Diet Assoc* 1998; **98**: 863.
- 24 Lawson O. The association of body weight, dietary intake, and energy expenditure with dietary restraint and disinhibition. *Obes Res* 1995; **3**: 153.
- 25 Boerner LM, Spillane NS, Anderson KG, Smith GT. Similarities and differences between women and men on eating disorder risk factors and symptom measures. *Eat Behav* 2004; **5**: 209.
- 26 Brown K, Bryant E, Naslund E, King N, Blundell J. Traits that promote weight gain in obesity, bulimia nervosa and EDNOS. *Obes Rev* 2006; **7**: 330.
- 27 Bryant EJ, King NA, Blundell JE. Disinhibition: its effects on appetite and weight regulation. *Obes Rev* 2007; **9**: 409–419.
- 28 Conus F, Allison DB, Rabasa-Lhoret R, St-Onge M, St-Pierre DH, Tremblay-Lebeau A *et al.* Metabolic and behavioral characteristics of metabolically obese but normal-weight women. *J Clin Endocrinol Metab* 2004; **89**: 5013–5020.
- 29 d'Amore A, Massignan C, Montera P, Moles A, De Lorenzo A, Scucchi S. Relationship between dietary restraint, binge eating, and leptin in obese women. *Int J Obes* 2001; **25**: 373–377.
- 30 St-Pierre D, Faraj M, Karelis A, Conus F, Henry J, St-Onge M *et al.* Lifestyle behaviours and components of energy balance as independent predictors of ghrelin and adiponectin in young non-obese women. *Diabetes and Metab* 2006; **32**: 131–139.
- 31 Flint A, Moller BK, Raben A, Sloth B, Pedersen D, Tetens I *et al.* Glycemic and insulinemic responses as determinants of appetite in humans. *Am J Clin Nutr* 2006; **84**: 1365–1373.
- 32 Riccardi G, Rivellese AA, Giacco R. Role of glycemic index and glycemic load in the healthy state, in prediabetes, and in diabetes. *Am J Clin Nutr* 2008; **87**: 269S–274S.
- 33 Weickert MO, Mohlig M, Spranger J, Schofl C, Loeffelholz CV, Reipl RL *et al.* Effects of euglycemia hyperinsulinemia and lipid infusion on circulating cholecystokinin. *J Clin Endocrinol Metab* 2008; **93**: 2328–2333.
- 34 Schneeman B. Dietary fiber and gastrointestinal function. *Nutr Res* 1998; **18**: 625–632.
- 35 Burton-Freeman B. Dietary fiber and energy regulation. *J Nutr* 2000; **130**: 272–278.
- 36 Burton-Freeman B, Davis PA, Schneeman BO. Plasma cholecystokinin is associated with subjective measures of satiety in women. *Am J Clin Nutr* 2002; **76**: 659–667.